The Need for Guidance on Immunotoxicity Risk Assessment

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Historical Background

[Select events impacting the potential development of immunotoxicology risk assessment guidance]

1995 — EPA's Health Effects Research Lab considers guidelines for immunotoxicology risk assessment

[Concludes that testing guidelines are necessary step toward risk assessment guidelines]

1996 — OPPTS releases test guideline for immunotoxicity (OPPTS 880.3550) and immune response (OPPTS 880.3800)

[EPA's guidelines are among earliest regulatory test guidelines; http://www.epa.gov/opptsfrs/OPPTS_Harmonized/880_Biochemicals_Test_Guidelines/]

1997

1998 — OPPTS publishes "Health Effects Test Guidelines: OPPTS 870.7800 Immunotoxicity"

[EPA's current testing guideline is part of the harmonized health effects test guidelines; http://www.epa.gov/opptsfrs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/870-7800.pdf]

1999

2000 — Food and Drug Administration (FDA) releases draft testing guideline on immunotoxicity for foods

[Published as part of "Redbook 2000"]

2001 — FDA releases immunotoxicity testing guideline for drugs

["Guidance for Industry: Immunotoxicity Evaluation of Investigational New Drugs"]

2002 — "Immunotoxicology in Risk Assessment" session at the *Toxicology and Risk Assessment Conference* discusses risk assessment in challenging areas of immunotoxicology

[Scientists from EPA, FDA, National Institute for Occupational Safety and Health (NIOSH), and industry give presentations on the state of the science in a conference sponsored by EPA, NIOSH, Agency for Toxic Substances and Disease Registry (ATSDR, and Tri-Service Toxicology (Air Force, Navy, and Army)]

EPA proposes changes to 40 CFR Part 158 that would require immunotoxicity testing for all conventional chemical pesticides

[EPA released proposed changes for public comment]

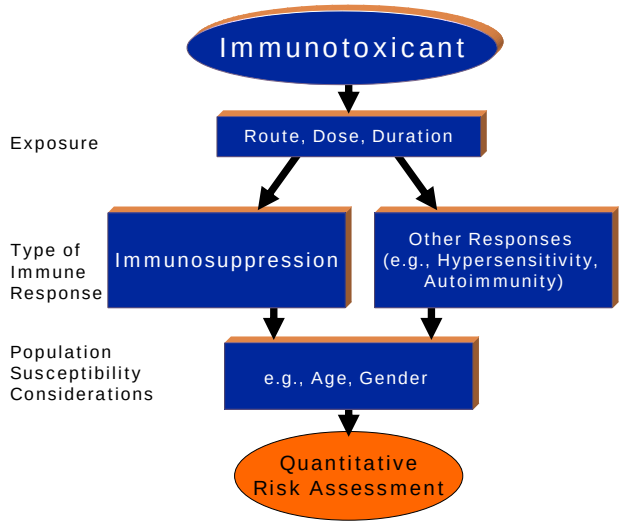
2003 — International Committee on Harmonization issues guidance for immunotoxicity testing for pharmaceuticals

["Guidance for Industry: S8 Immunotoxicity Studies for Human Pharmaceuticals"]

2004 2005 2006

The Need for Guidance

- Some chemicals act as immunotoxicants and result in altered immune function with the potential for adverse effects
- EPA has no Agency-wide guidance on incorporating immunotoxicity data into a chemical risk assessment
- Immunotoxicity data are often part of a chemical's toxicity dataset available to EPA, and may become more common
  - Health assessments for the chemicals in the Integrated Risk Information System (IRIS) evaluate the risk for immunotoxicity when immune response data are present
  - Although some Offices, such as OPP can request immunotoxicology studies, data <u>are not required</u> in all cases
  - Under proposed changes to Part 158 of title 40 of the Code of Federal Regulations (CFR) immunotoxicity testing (OPPTS 870.7800) would be <u>required</u> for all conventional pesticides
- Guidance would be valuable for the interpretation of immunotoxicity data for risk assessment



Strategy to Address the Need

- Create Technical Panel for Immunotoxicology Risk Assessment under EPA's Risk Assessment Forum
  - Use small groups for writing and to focus on key issues
  - Use full panel to address utility of draft guidance to EPA Program Offices

- Subcategories of immunotoxicology present diverse potential consequences of chemical immunotoxicity, such as:
  - **Immunosuppression** - *increased incidence and/or severity of infectious and neoplastic diseases*
  - **Hypersensitivity** - *allergy/asthma*
  - **Autoimmunity** - *autoimmune disease*
- There is more consensus in immunosuppression research and publications as to the state of the science for exposure considerations, measures of immunotoxicology, and other factors necessary for quantitative risk assessment than other areas of immunotoxicology
- The panel will begin with Immunosuppression Risk Assessment Guidance

Challenges

- Some of the challenges to be addressed
  1) Determine how subcategories of immunotoxicology (i.e., immunosuppression, hypersensitivity, etc.) would be addressed in a guidance document
  2) Application of short-term exposures to chronic risk assessment paradigms
  3) Distinguishing adverse immune responses from non-adverse
  4) Addressing susceptible populations

- Guidance for immunotoxicology risk assessment will address issues of exposure duration such as:
  - **28-day studies** – *the standard antibody production test (a test of immune function) utilizes a 28-day exposure*
  - **IRIS health assessments** – *for noncarcinogenic effects including immunotoxicology, IRIS files are of chronic health hazard assessment*

- A number of factors will contribute to the difficulty in distinguishing between adverse and non-adverse immune response, such as:
  - *Many measures of immune function have a large range within the population or large variation over time within the same individual*
  - *Functional overlap within the immune system*

- Some susceptible populations and/or lifestages have been described for immunotoxicology such as:
  - **The young** – *developmental immunotoxicology data suggest that developing individuals may be qualitatively or quantitatively more sensitive to immunotoxicants than adults*
  - **The aged** – *some measures of immune function may decline in older animals*

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